Tech Coloproctol (2006) 10:187–191
DOI 10.1007/s10151-006-0278-x

ORIGINAL ARTICLE

M. Salum • S.D. Wexner • J.J. Nogueras • E. Weiss • M. Koruda • K. Behrens • S. Cohen • S. Binderow J. Cohen • A. Thorson • C. Ternent • M. Christenson • G. Blatchford • V. Pricolo • M. Whitehead K. Doveney • J. Reilly • E. Glennon • S. Larach • P. Williamson • J. Gallagher • A. Ferrara • F. Harford R. Fry • T. Eisenstat • J. Notaro • B. Chinn • L. Yee • M. Stamos • P. Cole • G. Dunn • A. Singh • and the Program Directors Association in Colon and Rectal Surgery

Does sodium hyaluronate- and carboxymethylcellulose-based bioresorbable membrane (Seprafilm) decrease operative time for loop ileostomy closure?

Received: 31 January 2005 / Accepted: 27 March 2006 / Published online: 20 September 2006

Podium presentation at the annual meeting of the American Society of Colon and Rectal Surgeons, 2–5 June 2002, Chicago, IL, USA

M. Salum • S.D. Wexner (✉) • J.J. Nogueras • E. Weiss
Cleveland Clinic Florida
2950 Cleveland Clinic Blvd
Weston, FL 33331, USA
E-mail: mcderme@ccf.org

M. Koruda • K. Behrens
University of North Carolina
Chapel Hill, NC, USA

S. Cohen • S. Binderow • J. Cohen
Atlanta Colon and Rectal Surgery Department
Atlanta, GA, USA

A. Thorson • C. Ternent • M. Christenson • G. Blatchford
Colon and Rectal Surgery
Omaha, NE, USA

V. Pricolo
University Surgical Associates
Providence, RI, USA

M. Whitehead • K. Doveney
Oregon Health Sciences University
Portland, OR, USA

J. Reilly • E. Glennon
Colon and Rectal Surgery Department
Erie, PA, USA

S. Larach • P. Williamson • J. Gallagher • A. Ferrara
Colon and Rectal Clinic
Orlando, FL, USA

F. Harford
Loyola University of Chicago
Maywood, IL, USA

R. Fry
Thomas Jefferson University
Philadelphia, PA, USA

T. Eisenstat • J. Notaro • B. Chinn
Associates of Colon and Rectal Surgeons
Edison, NJ, USA

L. Yee
California Pacific Medical Center
San Francisco, CA, USA

M. Stamos
Harbor UCLA Medical Center
Torrence, CA, USA

P. Cole • G. Dunn
Colon and Rectal Associates
Shereport, LA, USA

A. Singh
State University of New York
Buffalo, NY, USA

Abstract Background Adhesions can result in serious clinical complications and make ileostomy closure, which is relatively simple procedure into a complicated and prolonged one. The use of sodium hyaluronate and carboxymethyl cellulose membrane (Seprafilm®) was proven to significantly reduce the postoperative adhesions at the site of application. The aim of this study was to assess the incidence and severity of adhesions around a loop ileostomy and to analyze the lenght of time and morbidity for mobilization at the time of ileostomy closure with and without the use of Seprafilm. **Methods** Twenty-nine surgeons from 15 institutions participated in this multicenter prospective randomized study. 191 patients with loop ileostomy construction were randomly assigned to either receive Seprafilm under the midline incision and around the stoma (Group I), only under the midline incision (Group II), or not to receive Seprafilm (Group III). At ileostomy closure, adhesions were quantified and graded; operative morbidity was also measured. **Results** All 3 groups were comparable relative to gender, mean age and number of patients with prior operations (26, 25 and 19, respectively). Group II patients were significantly more likely to have pre-existing adhesions than Group III patients (30.6% vs. 14.1%, p=0.025). At stoma mobilization, significantly more patients in Group III than in Group I had adhesions around the stoma (95.2% vs. 82.3%, p=0.021). Mean operative times were 27, 25, and 28 minutes, respectively (p=0.38), with significant differences among sites. There was no significant difference in the number of patients needing myotomy or enterotomy (29, 27 and 24 patients, respectively), nor in the number of postoperative complications (7, 9 and 7 patients, respectively). **Conclusions** When consistently applied, Seprafilm significantly decreased adhesion formation around the stoma but not operative times without any increase in the need for myotomy or enterotomy. These findings were not seen in the overall study population possibly due to the large number of surgeons using a variety of application techniques.

Key words Bioresorbable membrane • Sodium hyaluronate • Carboxymethylcellulose • Complications • Adhesions • Loop ileostomy

Introduction

Postoperative intra-abdominal adhesions are a result of trauma to the peritoneum, they develop after all types of surgery, and wee proven to prolong th operative time, increase the technical difficulty, and cause complications [1–4]. The socioeconomic burden related to adhesions is mostly caused by intestinal obstruction [5], while additional expenses may be related to the extra time required to gain entry to a peritoneal cavity in patients who have previously undergone surgery [6–8].

A membrane composed of modified sodium hyaluronate and carboxymethylcellulose (Seprafilm; Genzyme, Cambridge, MA) has been shown, through clinical and animal studies, to be safe and to significantly reduce the incidence, extent and severity of postoperative abdominal adhesions at the site of application [9–12]. It has also been recently demonstrated to lower small bowel obstruction after intestinal resection [13].

Loop ileostomy is relatively easy to create and to close, and is associated with an acceptable morbidity [14–16]. Therefore, creation of a defunctioning ileostomy is the procedure of choice for temporary fecal diversion for complex colorectal surgery in many centers. This study aimed to assess if placement of Seprafilm around a loop ileostomy reduced the incidence and severity of adhesions and reduced the length of time and morbidity for mobilization at ileostomy closure.

Patients and methods

Twenty-nine surgeons from 15 institutions participated in this multicenter, prospective randomized study. The study was approved by the Institutional Review Board (IRB) Patients underwent temporary loop ileostomy creation through a midline incision after restorative proctectomy, coloproctostomy or restorative proctocolectomy for any diagnosis. Enrollment was open from February 1998 to January 2001. Patients with carcinoma were excluded after December 1998. One hundred ninety-one patients were randomly assigned to one of three groups: Group I patients received Seprafilm under the midline incision and around the stoma; Group II patients received Seprafilm only under the midline incision; and Group III patients did not receive Seprafilm. Randomization was based on a computer-generated numeric sequence in sealed envelopes. The membrane was placed to cover the entire 360 degrees around the stoma including both limbs of small bowel.

At ileostomy closure, typically 6–8 weeks later, the surgeon evaluated adhesions by grade of severity. The severity grading followed a four-point grading system: grade 0, absence of adhesions; grade 1, filmy thickness, avascular; grade 2, moderate thickness, limited vascularity; and grade 3, dense thickness, well-vascularized. The numbers of previous abdominal operations and pre-existing adhesions were documented. Surgical data included the operative time, need for enterotomy or myotomy during stoma mobilization, and postoperative complications.

Statistical analysis

The data were statistically analyzed for significant differences using a one-way ANOVA. The Department of Biostatistics and Epidemiology at Cleveland Clinic Foundation calculated that to detect a 10-minute decrease in operative time for ileostomy closure with significance of $p<0.05$, 64 patients in each group yielded 90% power. For the continuous variables, data were compared using the Kruskal-Wallis test. Analyses of discrete variables was done using chi-squared test.

Results

A total of 191 patients was randomized to receive Seprafilm under the midline incision and around the stoma (Group I, 65 patients) or only under the midline incision (Group II, 62 patients) or to a negative control group (Group III, 64 patients). All three groups were comparable regarding gender, age, and number of patients who had prior operations (Table 1). During creation of the loop ileostomy, we observed a significantly greater number of patients in Group II with pre-existing adhesions than in Group III (30.6% vs. 14.1%, respectively; p=0.025). The mean operative times were 27 minutes in Group I, 25 min in Group II, and 28 minutes in Group III (p=0.38), although there were significant differences among sites (data not shown).

Data on stoma closure were available for 185 (97%) of the patients; data were unavailable for 6 patients for the following reasons: one patient had a stroke and died before closure, two patients needed a laparotomy for pouch excision, one patient had the stoma closed outside of the original hospital where he was treated, and two patients had small bowel obstruction and had their stomas closed during laparotomy. At stoma closure, adhesions around the stoma were found in significantly more patients in Group III than in Group I (95.2% vs. 82.3%, respectively; p=0.021) (Table 2). The need for entero- or myotomy was not significantly different among groups.

Postoperative complications occurred in 7 patients (10.7%) in Group I, 9 patients (14.5%) in Group II and 7 patients (10.9%) in Group III, without significant differences (p=0.77) (Table 3).

Table 1 Characteristics of 191 patients who underwent loop ileostomy, by study group

	Group I (n=65)	Group II (n=62)	Group III (n=64)	p
Age, years[a]	42.3 (18–78)	43.6 (18–73)	41.5 (20–84)	0.83*
Female, n (%)	32 (49.2)	26 (41.9)	26 (40.6)	0.57*
Number of patients with previous abdominal surgery, n (%)	26 (40.0)	25 (40.3)	19 (29.7)	0.37*
Number of patients with pre-existing adhesions, n (%)	17 (26.1)	19 (30.6)	9 (14.1)	0.025‡

*Kruskal-Wallis test; ‡Chi-square test for the comparison group II vs. III; [a] Values are mean (range)

Table 2 Grade of adhesions around the ileostomy and need for enterotomy or myotomy during stoma mobilization, for 185 of 191 patients, by study group. Values are number (percentage) of patients

	Group I	Group II	Group III
Adhesion grade			
0	11 (17.7)*	8 (13.3)‡	3 (4.8)
1	24 (38.7)	17 (28.3)	22 (34.9)
2	14 (22.6)	17 (28.3)	17 (27.0)
3	12 (19.4)	18 (30.0)	21 (33.3)
Enterotomy or myotomy	29 (46.8)	27 (45.0)	24 (38.1)
Total	62	60	63

*p=0.021 - Group I vs. Group III; ‡ p=0.096 - Group II vs. Group III, both done with chi-square test

Table 3 Postoperative complications recorded in 191 patients who had temporary loop ileostomy, by study group

Complication	Group I	Group II	Group III	Total
Small bowel obstruction	1	5	3	9
Prolonged ileus	1	1	1	3
Anastomotic leak	0	1	0	1
Parastomal abscess	0	1	0	1
Pouch abscess	0	1	0	1
Fistula	1	0	0	1
Pouch excision	1	0	0	1
Laparotomy to close stoma	2	0	0	2
Stroke	0	0	1	1
Dehydration	1	0	0	1
Deep vein thrombosis	0	0	1	1
High output ileostomy	0	0	1	1
Total	7 (10.7%)	9 (14.5%)	7 (10.9%)	23 (12.0%)

Discussion

There were multiple shortcomings within this study which may have affected its outcome. Specifically, the study included a large number of surgeons which resulted in a wide variability in surgical experience with the use of Seprafilm, the method of adhesion assessment and, importantly, the operative time for stoma mobilization. Moreover, there was a lack of stratification of patients for the incidence and extent of pre-existing adhesions. Although patients were randomly assigned to one of the three groups, statistical analyses demonstrated that the control group was not well-matched to the study groups in that significantly fewer patients had pre-existing adhesions. Third, the small number of patients enrolled per surgeon due to the competing Genzyme Outcomes Trial necessitated a lengthy accrual period and a larger number of surgeons than originally intended; these variables are important and could have accounted for the lack of statistical significance between treatments in this study. Fourth, although the original inclusion criteria included patients with rectal cancer, the study sponsor changed this diagnosis to an exclusion criteria effective December 1998; this change again necessitated the recruitment of more surgeons to participate in the trial, further confounding data purity and analysis. Fifth, neither the actual cost nor the cost-effectiveness was evaluated; these data would have been useful in order to make recommendations for future Seprafilm use. Finally, the use of immunosuppressive drugs was not recorded. A significant number of the patients with ulcerative colitis were on immunosuppressive medications at the time of surgery, which may have affected their outcomes.

Although Seprafilm significantly decreased adhesion formation around the stoma, the length of operative time for mobilization was not reduced. Moreover, there was no change in morbidity, including the need for enterotomy and myotomy. These findings may be attributed to a large number of surgeons using various techniques for application of Seprafilm and some outliers in operative times.

Acknowledgements We thank the Department of Biostatistics and Epidemiology at the Cleveland Clinic Foundation, Cleveland, Ohio for help in statistical analysis. This work was funded by Genzyme Corporation, Cambridge, MA, USA.

References

1. Scott-Coombes DM, Vipond MN, Thompson TN (1993) General surgeons' attitudes to the treatment and prevention of abdominal adhesions. Ann R Coll Surg Engl 75:123–128
2. Ellis H (1997) The clinical significance of adhesions: focus on intestinal obstruction. Eur J Surg Suppl 557:5–9
3. Menzies D, Ellis H (1990) Intestinal obstruction from adhesions: how big is the problem? Ann R Coll Surg 72:60–63
4. Monk BJ, Berman ML, Montz FJ (1994) Adhesions after extensive gynecologic surgery: clinical significance, etiology and prevention. Am J Obstet Gynecol 170:1396–1403
5. Ray NF, Larsen JW Jr, Stillman RJ, Jacobs RJ (1993) Economic impact of hospitalization for lower abdominal adhesiolysis in US in 1988. Surg Gynecol Obstet 176:271–276
6. Beck DE, Ferguson MA, Opelka FG et al (2000) Effect of previous surgery on abdominal opening time. Dis Colon Rectum 43:1749–1753
7. Coleman MG, McLain AD, Moran BJ (2000) Impact of previous surgery on time taken for incision and division of adhesions during laparotomy. Dis Colon Rectum 43:1297–1299
8. van der Krabben AA, Dijkstra FR, Nieuwenhuijzen M et al (2000) Morbidity and mortality of inadvertent enterotomy during adhesiotomy. Br J Surg 87:467–471
9. Becker JM, Dayton MT, Fazio VW et al (1996) Prevention of postoperative abdominal adhesions by a sodium hyaluronate-based bioresorbable membrane: a prospective, randomized, double-blind multicenter study. J Am Coll Surg 183:297–306
10. Salum MR, Lam DTY, Wexner SD et al (2001) Does limited placement of bioresorbable membrane of modified sodium hyaluronate and carboxymethylcellulose (Seprafilm) have possible short-term beneficial impact? Dis Colon Rectum 44:706–712
11. Moreira H Jr, Wexner SD, Yamaguchi T et al (2000) Use of bioresorbable membrane (sodium hyaluronate-carboxymethylcellulose) after controlled bowel injuries in a rabbit model. Dis Colon Rectum 43:182–187
12. Vrijland WW, Tseng LN, EiJkman HJ et al (2002) Fewer intraperitoneal adhesions with the use of hyaluronic acid-carboxymethylcellulose membrane: a randomized clinical trial. Ann Surg 235:193–199
13. Fazio VW, Cohen Z, Fleshman JW et al (2005) Reduction in adhesive small-bowel obstruction by Seprafilm. Adhesion barrier after intestinal resection. Dis Colon Rectum 49:1–11
14. Amin SN, Memon MA, Armitage NC, Scholefield JH (2001) Defunctioning loop ileostomy and stapled side-to-side closure has low morbidity. Ann R Coll Surg Engl 83:246–249
15. Edwards DP, Leppington-Clarke A, Sexton R et al (2001) Stoma-related complications are more frequent after transverse colostomy than loop ileostomy: a prospective randomized clinical trial. Br J Surg 88:360–363
16. O'Toole GC, Hyland JM, Grant DC, Barry MK (1999) Defunctioning loop ileostomy: a prospective audit. J Am Coll Surg 188:6–9

Invited comment

Thank you for asking me to comment on this paper which attempts to address the question of the use of Seprafilm as an adhesive preventative agent around loop ileostomy. The strategy of the paper is basically good in dividing the patient cohort into three groups, namely Group I, those in whom Seprafilm was placed under the

midline incision and around the stoma; Group II, those in whom Seprafilm was placed only around the stoma; and Group III, those in whom no Seprafilm was placed. Unfortunately, this division of itself demands large numbers of patients in the trial in order to achieve statistical significance. Since Seprafilm has already been shown to have an effect on the midline wound in terms of adhesion prevention, it might have been simpler to compare only Groups I and III.

Be that as it may, there are indeed basic problems with this paper in terms of numbers of patients recruited together with the fact that the trial is multicentric and includes many surgeons. In total, there are 32 authors from 15 separate institutions who operated on 191 patients. This means that, on average, individual surgeons operated on only 2 patients in each study group. The authors stated that there were some high volume centres, which by definition means that it is likely that some surgeons may have operated on 1 or less patients per group. However, to be fair to the authors, they do recognise these deficiencies in the paper.

The second major problem, again recognised by the authors, is the lack of stratification of patients for the incidence and extent of previous adhesions. There was a significantly lower number of adhesions in Group III patients than in Group II patients, which immediately confounds any interpretation of later results. However, my main criticism of the assessment of the adhesions is that this was not performed by an independent assessor. It is apparent that, with large numbers of surgeons in separate institutions, this would have been almost impossible but it serves to remind us all how difficult it can be to set up valid trials designed to assess anti-adhesion strategies which can stand up to intellectual scrutiny.

It is a shame that the study sponsor felt obliged to alter the recruitment criteria in December 1998 to exclude patients with colorectal cancer since this will also have had a bearing on the interpretation of the results of this trial. It simply introduces yet another variable such that direct comparison of the groups is no longer valid.

The authors also stated that neither cost nor cost-effectiveness was evaluated in this trial, which they feel might have been useful in order to make recommendations for future Seprafilm use. However, I would say that with the outcomes of this somewhat compromised study, which claims a reduction in numbers of patients with adhesions around stomas protected with Seprafilm and yet no reduction in the time taken for mobilisation nor any reduction in morbidity, one has to ask the question "what is the evidence that there is any clinical benefit to the patients at all?"

I do recognise that the authors have been scrupulously honest in their analysis and reporting of this trial, but I am obliged to say that this paper will have little impact on the assessment of Seprafilm as an adhesion prevention tool. The strategy of the trial is basically sensible but much larger numbers are required with more stringent controls as to the number of surgeons and centres involved and there must be no alteration to the recruitment once the trial is underway. Independent blinded video-analysis of the adhesions before and after treatment would be helpful in order to further enhance the analysis.

Trials to determine effectiveness of adhesion prevention strategies are notoriously difficult to design. This paper demonstrates that fact. I am sure the authors will reflect on the shortcomings of this particular paper and I do hope that they will strive to continue the work on Seprafilm which is justifiably recognised as an adhesion preventative but perhaps with more attention to trial design. It is vital to the scientific community that we acquire high quality, truly validated data on the use of such agents before we can make recommendations to introduce them to the surgical community as a routine part of the fight against adhesions.

M.C. Parker
Darent Valley Hospital
Dartford, UK